A

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QHVQELPVPLALPLEAATCKKYMAKLRTTVSAQSRFLSTYDGAETLCLEDIYTENVLEVWADVGMAGPPQKSPATLGLEELFSTPGHLNDDADTVLVVGE 300
AGSGKSTLLQRLHLLWAAGQDFQEFLFVFPFSCRQLQCMAKPLSVRTLLFEHCCWPDVGQEDIFQLLLDHPDRVLLTFDGFDEFKFRFTDRERHCSPTDP 400
TSVQTLLFNLLQGNLLKNARKVVTSRPAAVSAFLRKYIRTEFNLKGFSEQGIELYLRKRHHEPGVADRLIRLLQETSALHGLCHLPVFSWMVSKCHQELL 500
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SVGDIGVEQLLPCLGVCKALYLRDNNISDRGICKLIECALHCEQLQKLALFNNKLTDGCAHSMAKLLACRQNFLALRLGNNYITAAGAQVLAEGLRGNTS 900
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B

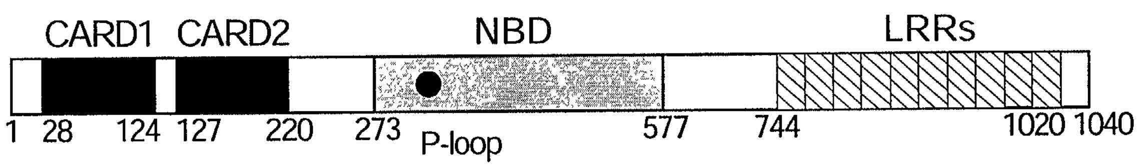
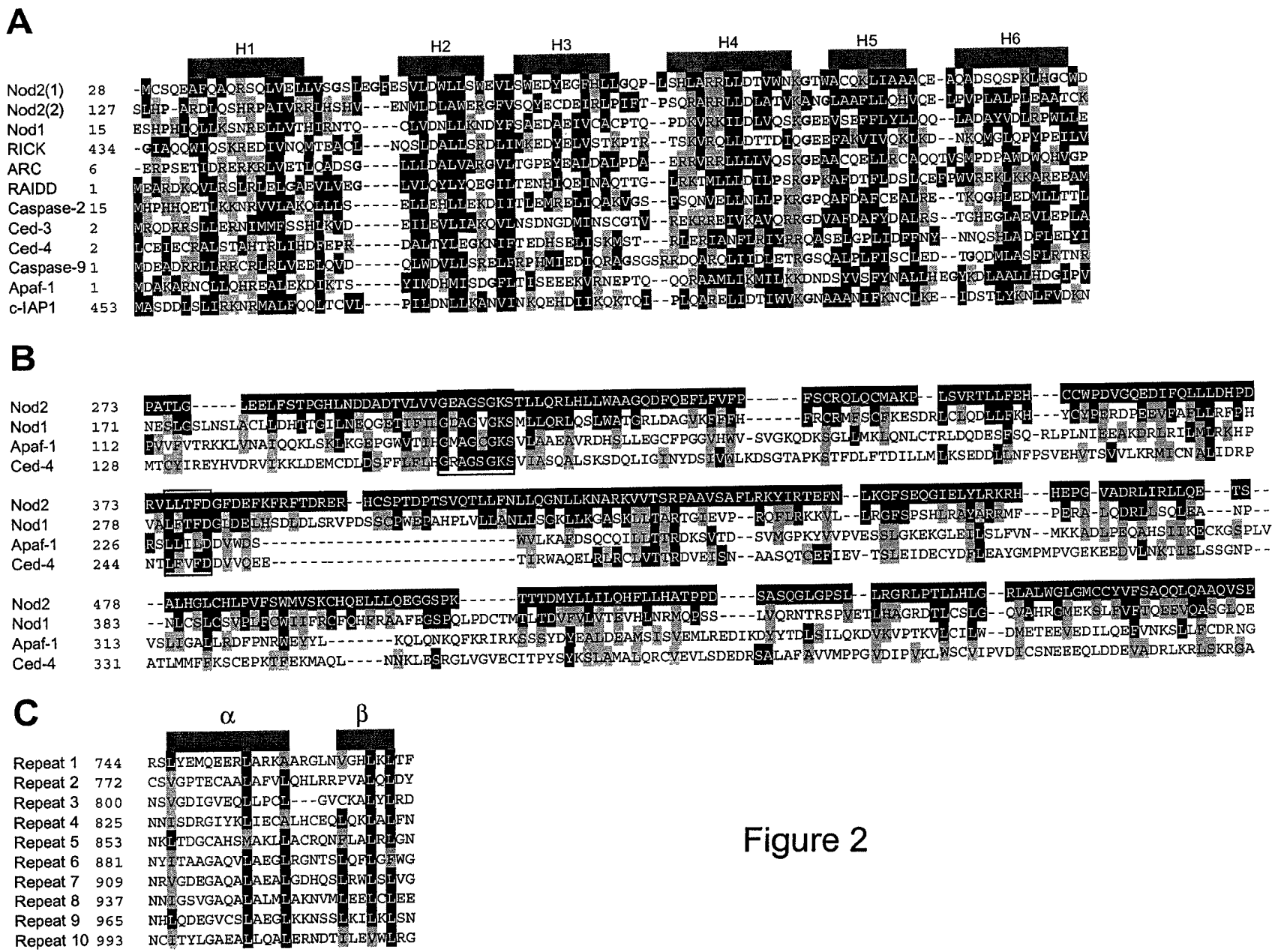


Figure 1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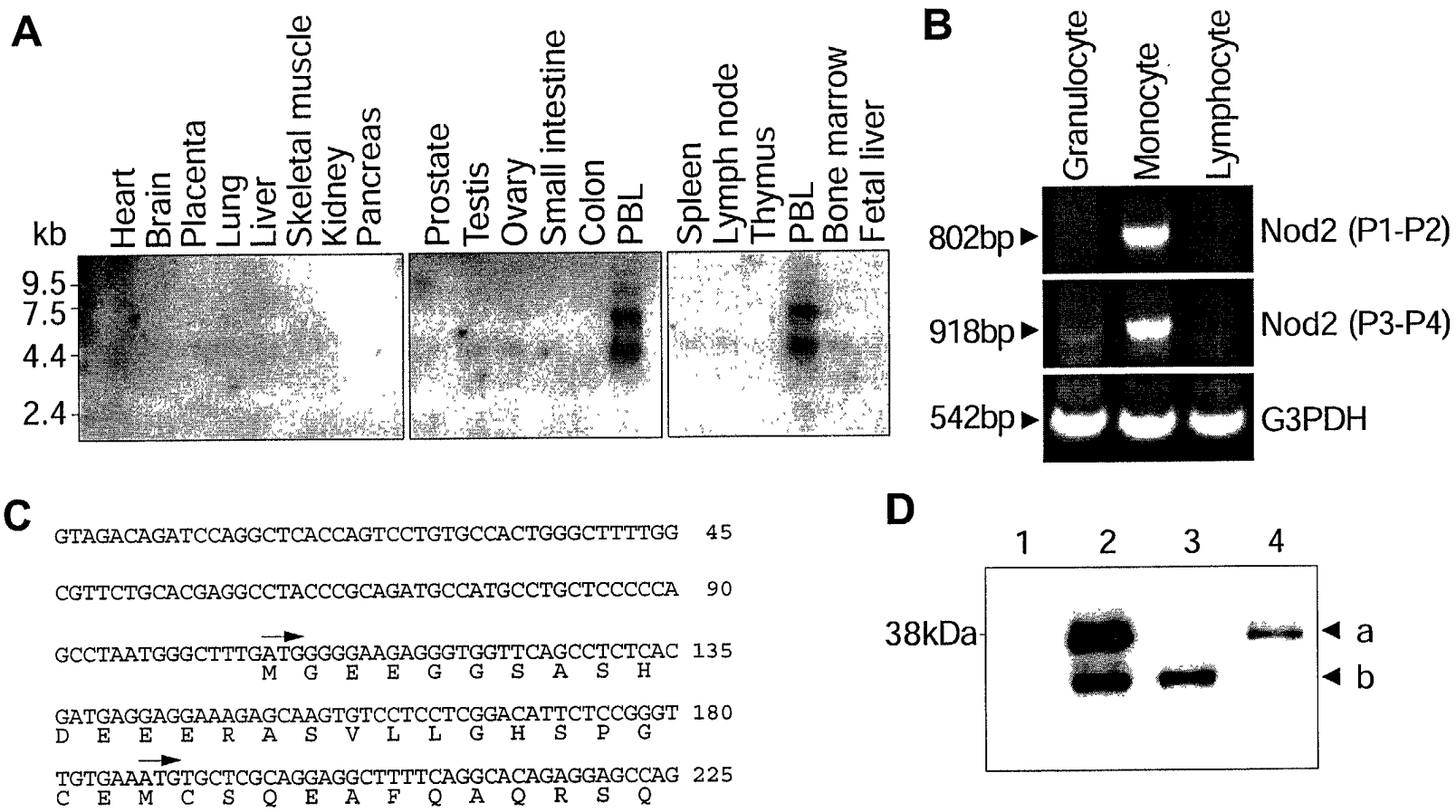
H1
H2
H3
H4
H5
H6
Nod2(1) 28
Nod2(2) 127
Nod1 15
RICK 434
ARC 6
RAIDD 1
Caspase-2 15
Ced-3 2
Ced-4 2
Caspase-9 1
Apaf-1 1
c-IAP1 453
B
Nod2 273
Nod1 171
Apaf-1 112
Ced-4 128
Nod2 373
Nod1 278
Apaf-1 226
Ced-4 244
Nod2 478
Nod1 383
Apaf-1 313
Ced-4 331
C
α
β
Repeat 1 744
Repeat 2 772
Repeat 3 800
Repeat 4 825
Repeat 5 853
Repeat 6 881
Repeat 7 909
Repeat 8 937
Repeat 9 965
Repeat 10 993

Figure 2



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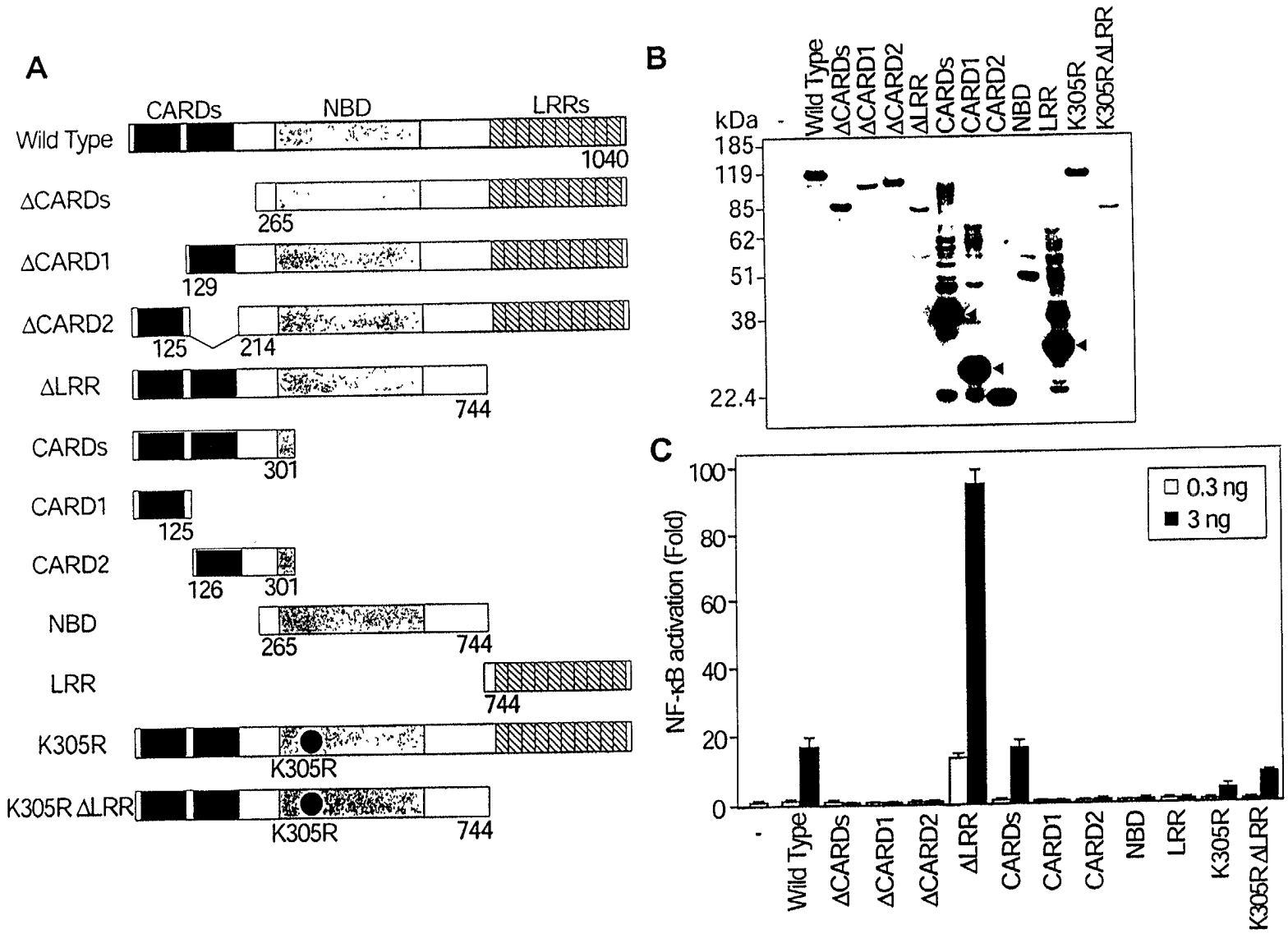
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CARDs
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LRRs
Wild Type
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ΔCARDs
265
ΔCARD1
129
ΔCARD2
125
214
ΔLRR
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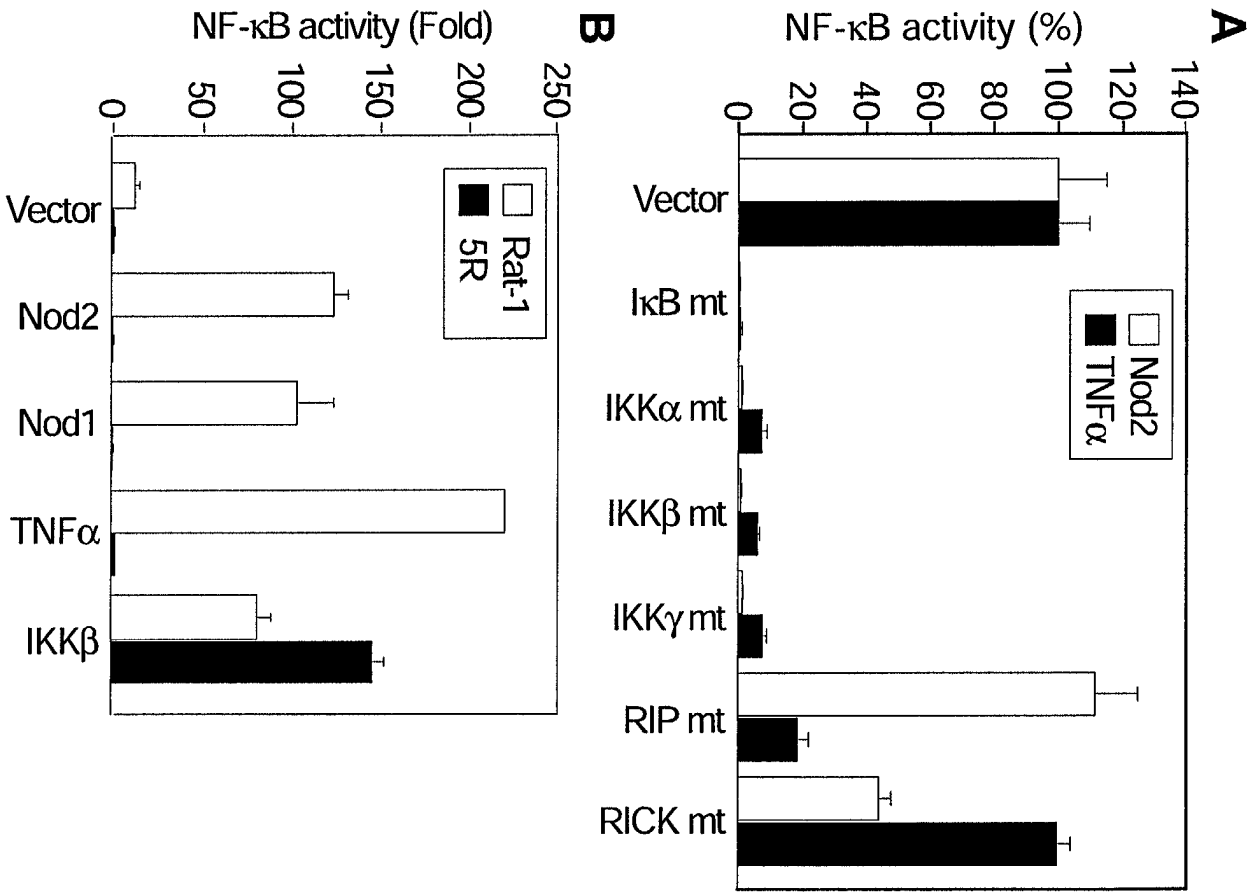
CARDs
301
CARD1
125
CARD2
126
301
NBD
265
744
LRR
744
K305R
K305R
K305R ΔLRR
K305R
744
B
kDa
Wild Type
ΔCARDs
ΔCARD1
ΔCARD2
ΔLRR
CARDs
CARD1
CARD2
NBD
LRR
K305R
K305R ΔLRR
185
119
85
62
51
38
22.4
C
NF-κB activation (Fold)
0.3 ng
3 ng
100
80
60
40
20
0
-
Wild Type
ΔCARDs
ΔCARD1
ΔCARD2
ΔLRR
CARDs
CARD1
CARD2
NBD
LRR
K305R
K305R ΔLRR

Figure 4



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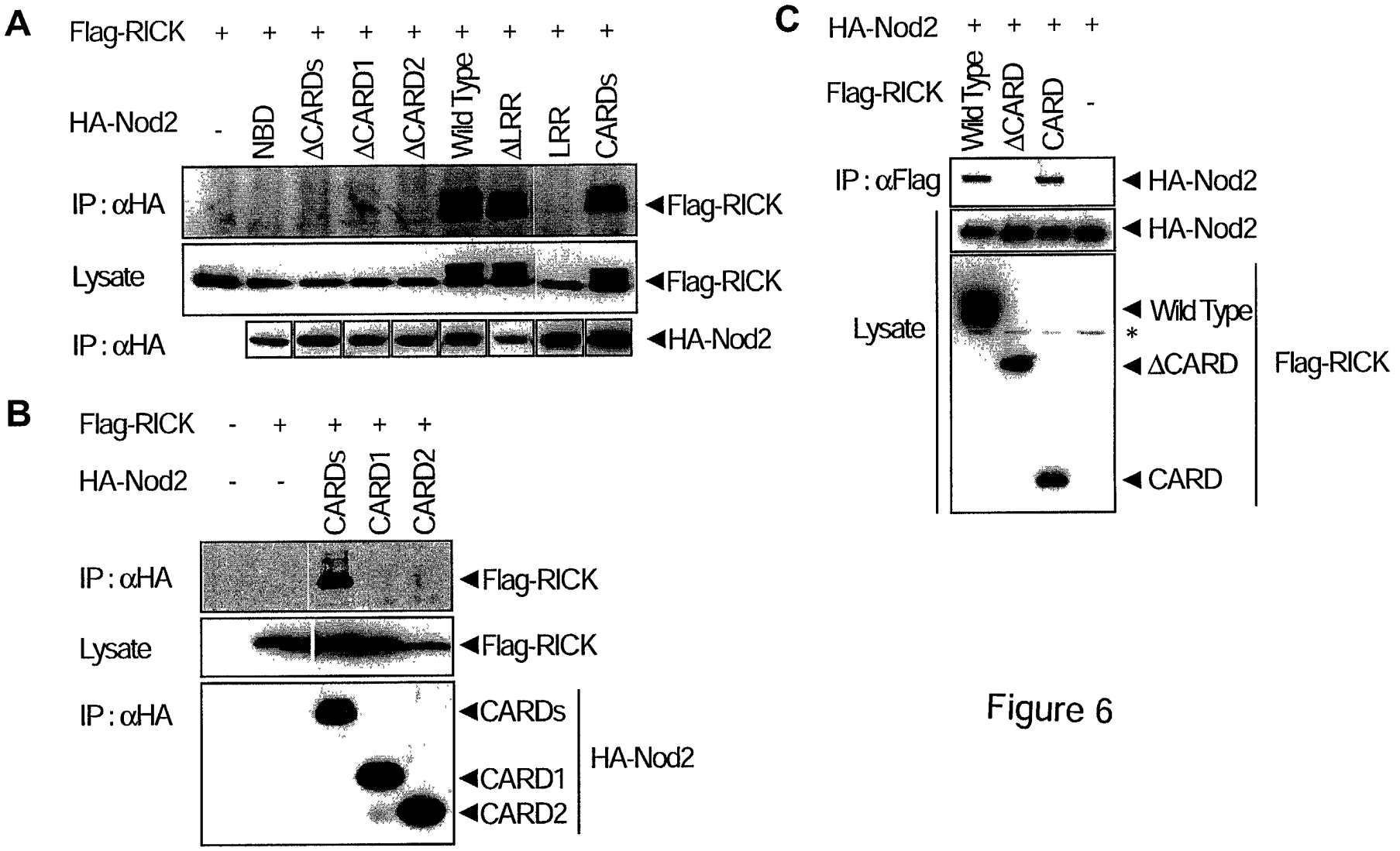

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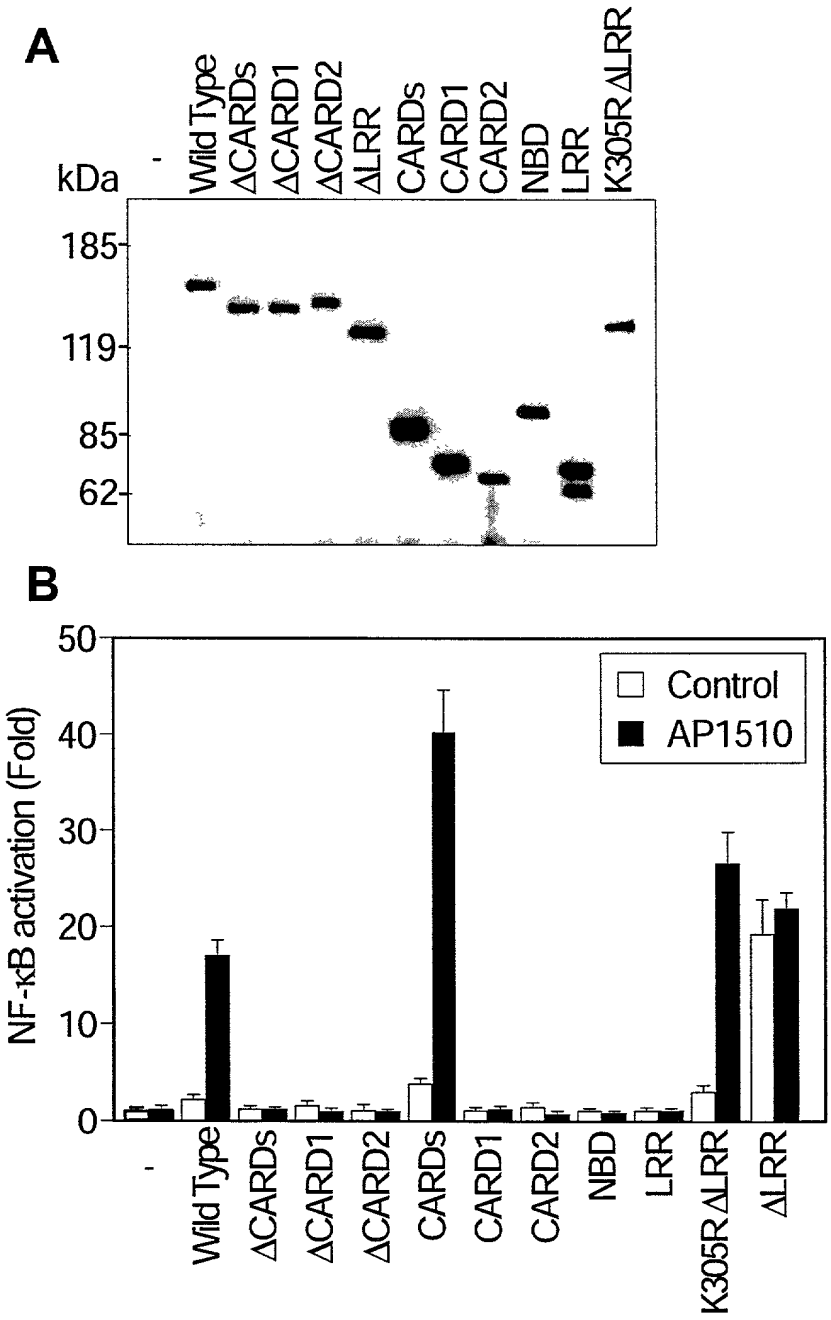
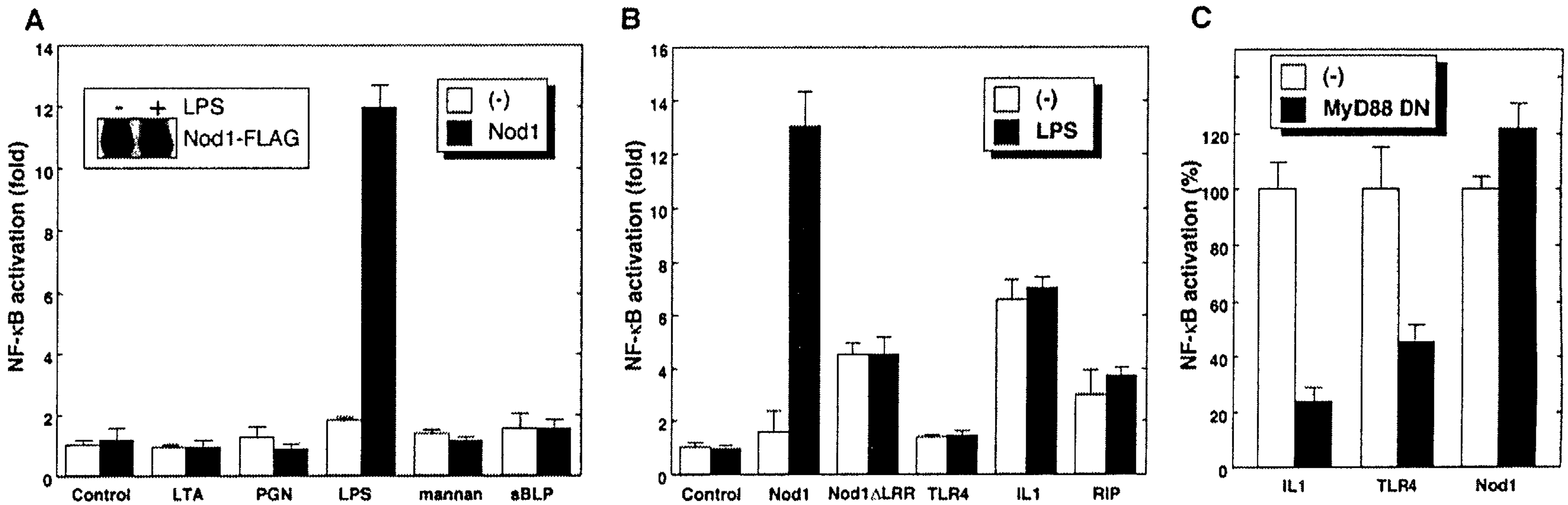

A
kDa
-
Wild Type
ΔCARDs
ΔCARD1
ΔCARD2
ΔLRR
CARDs
CARD1
CARD2
NBD
LRR
K305R ΔLRR
185
119
85
62
B
NF-κB activation (Fold)
50
40
30
20
10
0
Control
AP1510
-
Wild Type
ΔCARDs
ΔCARD1
ΔCARD2
ΔCARDs
CARD1
CARD2
NBD
LRR
K305R ΔLRR
ΔLRR

Figure 7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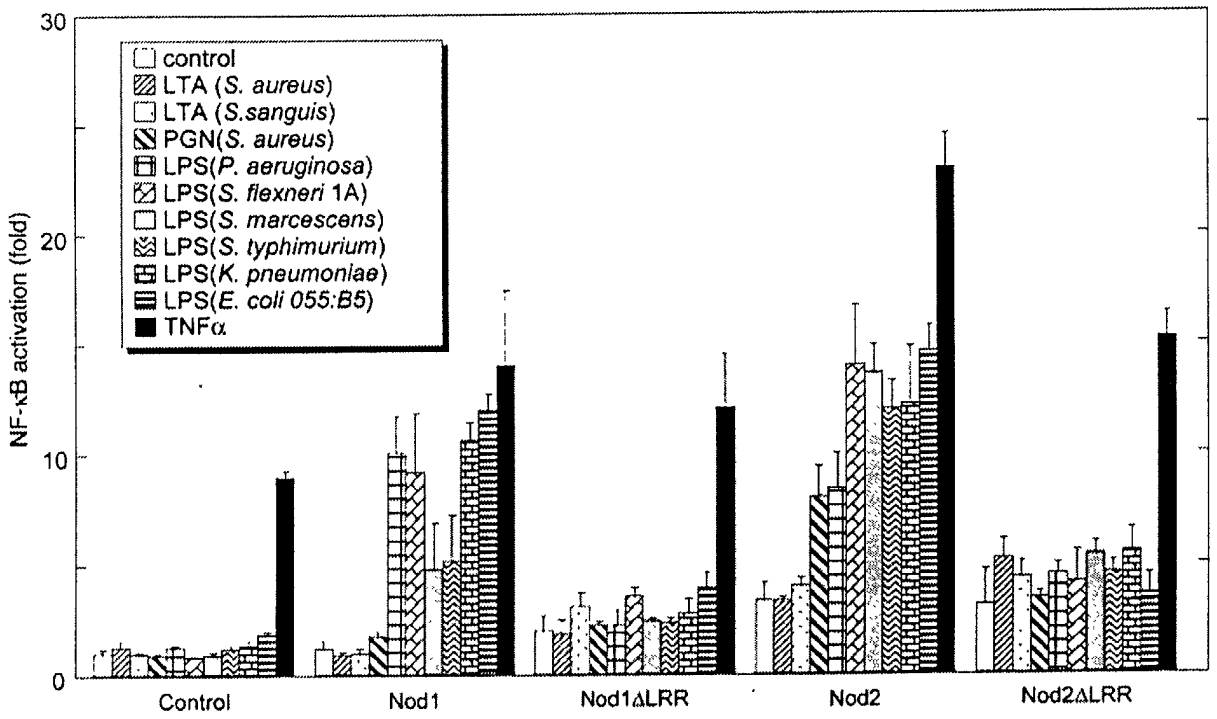
NF-κB activation (fold)
- + LPS
Nod1-FLAG
(-)
Nod1
Control
LTA
PGN
LPS
mannan
sBLP
B
NF-κB activation (fold)
(-)
LPS
Control
Nod1
Nod1ΔLRR
TLR4
IL1
RIP
C
NF-κB activation (%)
(-)
MyD88 DN
IL1
TLR4
Nod1

Figure 8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20
10
0
NF-κB activation (fold)
control
LTA (S. aureus)
LTA (S.sanguis)
PGN(S. aureus)
LPS(P. aeruginosa)
LPS(S. flexneri 1A)
LPS(S. marcescens)
LPS(S. typhimurium)
LPS(K. pneumoniae)
LPS(E. coli 055:B5)
TNFα
Control
Nod1
Nod1ΔLRR
Nod2
Nod2ΔLRR

Figure 9

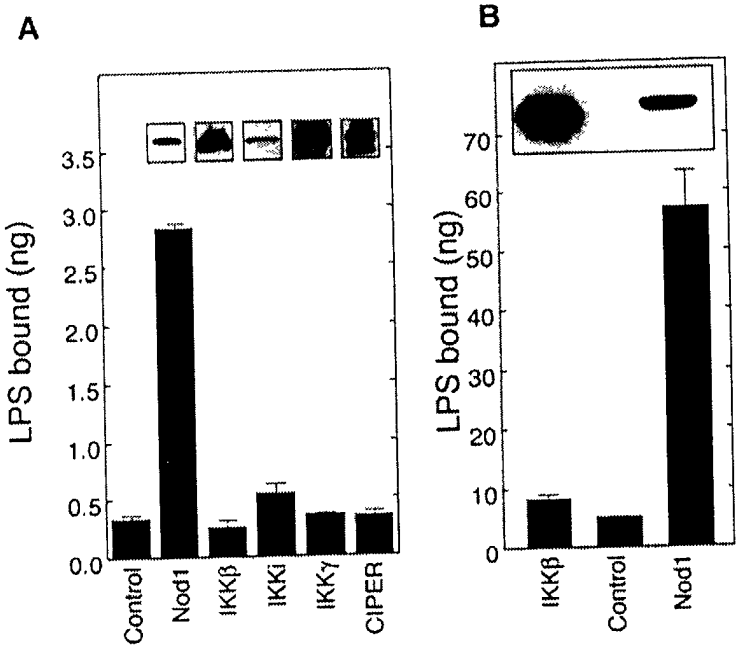

Figure 10

Figure 11

SEQ ID NO:33

Nod2 cDNA sequence

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ggttcagcct ctcacgatga ggaggaaaga gcaagtgtcc tcctcggaca ttctccgggt    180
tgtgaaatgt gctcgcagga ggcttttcag gcacagagga gccagctggt cgagctgctg    240
gtctcagggt ccctggaagg cttcgagagt gtcctggact ggctgctgtc ctgggaggtc    300
ctctcctggg aggactacga gggcttccac ctcctgggcc agcctctctc ccacttggcc    360
aggcgccttc tggacaccgt ctggaataag ggtacttggg cctgtcagaa gctcatcgcg    420
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cactcgctcc acccagcccg agacctgcag agtcaccggc cagccattgt caggaggctc    540
cacagccatg tggagaacat gctggacctg gcatgggagc ggggtttcgt cagccagtat    600
gaatgtgatg aaatcaggtt gccgatcttc acaccgtccc agagggcaag aaggctgctt    660
gatcttgcca cggtgaaagc gaatggattg gctgccttcc ttctacaaca tgttcaggaa    720
ttaccagtcc cattggccct gcctttggaa gctgccacat gcaagaagta tatggccaag    780
ctgaggacca cggtgtctgc tcagtctcgc ttcctcagta cctatgatgg agcagagacg    840
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ctctttgtct tcccattcag ctgccggcag ctgcagtgca tggccaaacc actctctgtg   1140
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Figure 12

SEQ ID NO:1

Nod2 cDNA sequence

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cactccagct gggatcacat gtggactttt atttccagtg aaatcagtta ctcttcagtt 4020

aagcctttgg aaacagctcg actttaaaaa gctccaaatg cagctttaaa aaattaatct 4080

gggccagaat ttcaaacggc ctcactaggc ttctggttga tgcctgtgaa ctgaactctg 4140

acaacagact tctgaaatag acccacaaga ggcagttcca tttcatttgt gccagaatgc 4200

tttaggatgt acagttatgg attgaaagtt tacaggaaaa aaaattaggc cgttccttca 4260

aagcaaatgt cttcctggat tattcaaaat gatgtatgtt gaagcctttg taaattgtca 4320

gatgctgtgc aaatgttatt attttaaaca ttatgatgtg tgaaaactgg ttaatattta 4380

taggtcactt tgttttactg tcttaagttt atactcttat agacaacatg gccgtgaact 4440

ttatgctgta aataatcaga ggggaataaa ctgttgagtc aaaac 4485

Figure 13

SEQ ID NO:2

MGEEGGSASH DEEERASVLL GHSPGCEMCS QEAFQAQRSQ LVELLVSGSL EGFESVLDWL
LSWEVLSWED YEGFHLLGQP LSHLARRLLD TVWNKGTWAC QKLIAAAQEA QADSQSPKLH
GCWDPHSLHP ARDLQSHRPA IVRRLHSHVE NMLDLAWERG FVSQYECDEI RLPIFTPSQR
ARRLLDLATV KANGLAAFLL QHVQELPVPL ALPLEAATCK KYMAKLRTTV SAQSRFLSTY
DGAETLCLED IYTENVLEVW ADVGMAGPPQ KSPATLGLEE LFSTPGHLND DADTVLVVGE
AGSGKSTLLQ RLHLLWAAGQ DFQEFLFVFP FSCRQLQCMA KPLSVRTLLF EHCCWPDVGQ
EDIFQLLLDH PDRVLLTFDG FDEFKFRFTD RERHCSPTDP TSVQTLLFNL LQGNLLKNAR
KVVTSRPAAV SAFLRKYIRT EFNLKGFSEQ GIELYLRKRH HEPGVADRLI RLLQETSALH
GLCHLPVFSW MVSKCHQELL LQEGGSPKTT TDMYLLILQH FLLHATPPDS ASQGLGPSLL
RGRLPTLLHL GRLALWGLGM CCYVFSAQQL QAAQVSPDDI SLGFLVRAKG VVPGSTAPLE
FLHITFQCFF AAFYLALSAD VPPALLRHLF NCGRPGNSPM ARLLPTMCIQ ASEGKDSSVA
ALLQKAEPHN LQITAAFLAG LLSREHWGLL AECQTSEKAL LRRQACARWC LARSLRKHFH
SIPPAAPGEA KSVHAMPGFI WLIRSLYEMQ EERLARKAAR GLNVGHLKLT FCSVGPTECA
ALAFVLQHLR RPVALQLDYN SVGDIGVEQL LPCLGVCKAL YLRDNNISDR GICKLIECAL
HCEQLQKLAL FNNKLTDGCA HSMAKLLACR QNFLALRLGN NYITAAGAQV LAEGLRGNTS
LQFLGFWGNR VGDEGAQALA EALGDHQSLR WLSLVGNNIG SVGAQALALM LAKNVMLEEL
CLEENHLQDE GVCSLAEGLK KNSSLKILKL SNNCITYLGA EALLQALERN DTILEVWLRG
NTFSLEEVDK LGCRDTRLLL *

Figure 14

SEQ ID NO:3

MCSQEAFQAQ RSQLVELLVS GSLEGFESVL DWLLSWEVLS WEDYEGFHLL GQPLSHLARR
LLDTVWNKGT WACQKLIAAA QEAQADSQSP KLHGCWDPHS LHPARDLQSH RPAIVRRLHS
HVENMLDLAW ERGFVSQYEC DEIRLPIFTP SQRARRLLDL ATVKANGLAA FLLQHVQELP
VPLALPLEAA TCKKYMAKLR TTVSAQSRFL STYDGAETLC LEDIYTENVL EVWADVGMAG
PPQKSPATLG LEELFSTPGH LNDDADTVLV VGEAGSGKST LLQRLHLLWA AGQDFQEFLF
VFPFSCRQLQ CMAKPLSVRT LLFEHCCWPD VGQEDIFQLL LDHPDRVLLT FDGFDEFKFR
FTDRERHCSP TDPTSVQTLL FNLLQGNLLK NARKVVTSRP AAVSAFLRKY IRTEFNLKGF
SEQGIELYLR KRHHEPGVAD RLIRLLQETS ALHGLCHLPV FSWMVSKCHQ ELLLQEGGSP
KTTTDMYLLI LQHFLLHATP PDSASQGLGP SLLRGRLPTL LHLGRLALWG LGMCCYVFSA
QQLQAAQVSP DDISLGFLVR AKGVVPGSTA PLEFLHITFQ CFFAAFYLAL SADVPPALLR
HLFNCGRPGN SPMARLLPTM CIQASEGKDS SVAALLQKAE PHNLQITAAF LAGLLSREHW
GLLAECQTSE KALLRRQACA RWCLARSLRK HFHSIPPAAP GEAKSVHAMP GFIWLIRSLY
EMQEERLARK AARGLNVGHL KLTFCSVGPT ECAALAFVLQ HLRRPVALQL DYNSVGDIGV
EQLLPCLGVC KALYLRDNNI SDRGICKLIE CALHCEQLQK LALFNNKLTD GCAHSMAKLL
ACRQNFLALR LGNNYITAAG AQVLAEGLRG NTSLQFLGFW GNRVGDEGAQ ALAEALGDHQ
SLRWLSLVGN NIGSVGAQAL ALMLAKNVML EELCLEENHL QDEGVCSLAE GLKKNSSLKI
LKLSNNCITY LGAEALLQAL ERNDTILEVW LRGNTFSLEE VDKLGCRDTR LLL*

Figure 15
SEQ ID NO:34

Nod2a AA sequence, Mutant

MGEEGGSASH DEEERASVLL GHSPGCEMCS QEAFQAQRSQ LVELLVSGSL EGFESVLDWL
LSWEVLSWED YEGFHLLGQP LSHLARRLLD TVWNKGTWAC QKLIAAAQEA QADSQSPKLH
GCWDPHSLHP ARDLQSHRPA IVRRLHSHVE NMLDLAWERG FVSQYECDEI RLPIFTPSQR
ARRLLDLATV KANGLAAFLL QHVQELPVPL ALPLEAATCK KYMAKLRTTV SAQSRFLSTY
DGAETLCLED IYTENVLEVW ADVGMAGPPQ KSPATLGLEE LFSTPGHLND DADTVLVVGE
AGSGKSTLLQ RLHLLWAAGQ DFQEFLFVFP FSCRQLQCMA KPLSVRTLLF EHCCWPDVGQ
EDIFQLLLDH PDRVLLTFDG FDEFKFRFTD RERHCSPTDP TSVQTLLFNL LQGNLLKNAR
KVVTSRPAAV SAFLRKYIRT EFNLKGFSEQ GIELYLRKRH HEPGVADRLI RLLQETSALH
GLCHLPVFSW MVSKCHQELL LQEGGSPKTT TDMYLLILQH FLLHATPPDS ASQGLGPSLL
RGRLPTLLHL GRLALWGLGM CCYVFSAQQL QAAQVSPDDI SLGFLVRAKG VVPGSTAPLE
FLHITFQCFF AAFYLALSAD VPPALLRHLF NCGRPGNSPM ARLLPTMCIQ ASEGKDSSVA
ALLQKAEPHN LQITAAFLAG LLSREHWGLL AECQTSEKAL LRRQACARWC LARSLRKHFH
SIPPAAPGEA KSVHAMPGFI WLIRSLYEMQ EERLARKAAR GLNVGHLKLT FCSVGPTECA
ALAFVLQHLR RPVALQLDYN SVGDIGVEQL LPCLGVCKAL YLRDNNISDR GICKLIECAL
HCEQLQKLAL FNNKLTDGCA HSMAKLLACR QNFLALRLGN NYITAAGAQV LAEGLRGNTS
LQFLGFWGNR VGDEGAQALA EALGDHQSLR WLSLVGNNIG SVGAQALALM LAKNVMLEEL
CLEENHLQDE GVCSLAEGLK KNSSLKILKL SNNCITYLGA EALLQAP*

FIGURE 16

Nod2 Exon11, Wild type

cagacatgag caggatgtgt ctaagggaca ggtgggcttc agtagactgg ctaactcctg

cagtctcttt aactggacag tttcaagagg aaaaccaaga atccttgaag ctcaccattg

tatcttcttt tccagGTTGT CCAATAACTG CATCACCTAC CTAGGGGCAG AAGCCCTCCT

L S N N C I T Y L G A E A L L

GCAGGCCCTT GAAAGGAATG ACACCATCCT GGAAGTCTGg taaggcccct gggcaggcct

Q A L E R N D T I L E V

gttttagctc tccgaacctc agtttttcta tctgtaaaat ggggtgacgg gagagaggaa

tggcagaatt ttgaggatcc cttctgattc tgacattcag tgagaatgat tctgcatgtg

Nod2 Exon11, Mutant

cagacatgag caggatgtgt ctaagggaca ggtgggcttc agtagactgg ctaactcctg

cagtctcttt aactggacag tttcaagagg aaaaccaaga atccttgaag ctcaccattg

tatcttcttt tccagGTTGT CCAATAACTG CATCACCTAC CTAGGGGCAG AAGCCCTCCT

L S N N C I T Y L G A E A L L

GCAGGCCCCT TGAAAGGAAT GACACCATCC TGGAAGTCTG gtaaggcccc tgggcaggcc

Q A P *

tgttttagct ctccgaacct cagtttttct atctgtaaaa tggggtgacg ggagagagga

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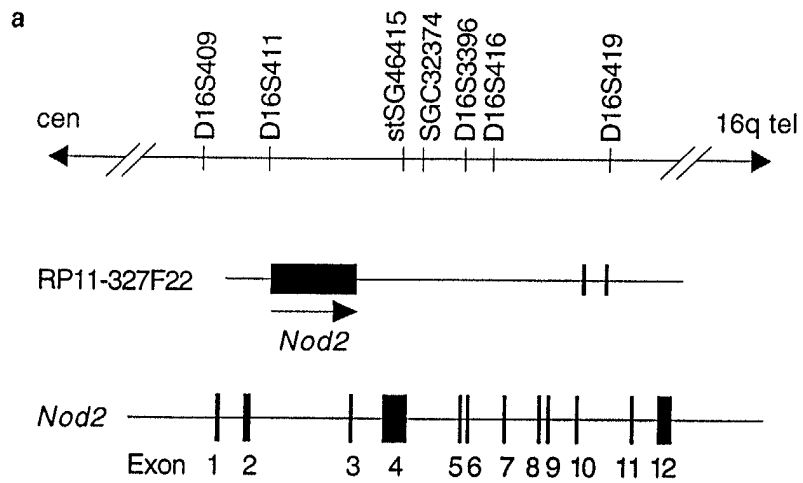
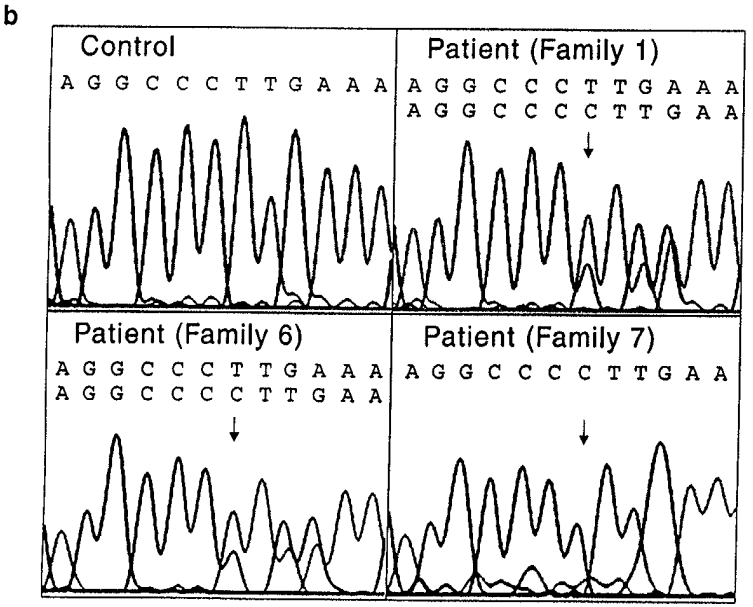
g





c

Wild-type

TCTTTTCCAGGTTGTCCAATAACTGCATCACCTACCTAGGGGCAGAAGCC
L S N N C I T Y L G A E A

CTCCTGCAGGCCCTTGAAAGGAATGACACCATCCTGGAAGTCTGGTAAGG
L L Q A L E R N D T I L E V (W)

3020InsC

TCTTTTCCAGGTTGTCCAATAACTGCATCACCTACCTAGGGGCAGAAGCC
L S N N C I T Y L G A E A

CTCCTGCAGGCCCCTTGAAAGGAATGACACCATCCTGGAAGTCTGGTAAG
L L Q A P *

d

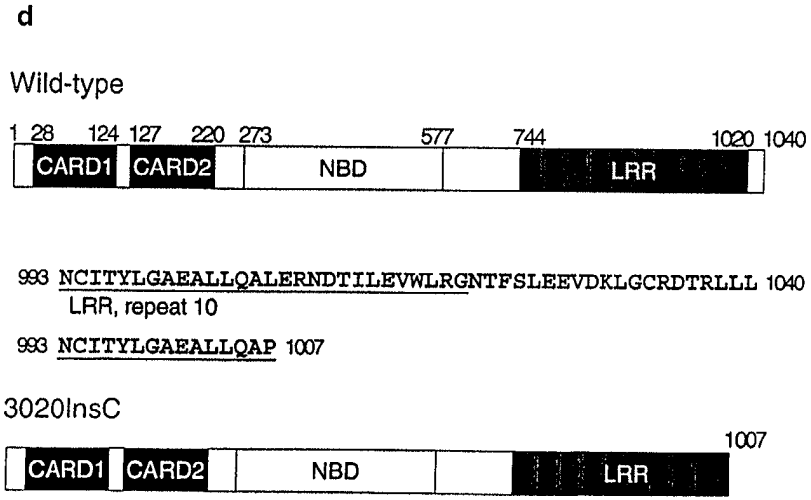


Figure 17

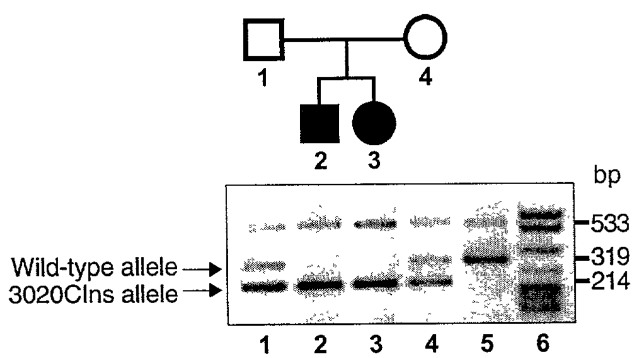


Figure 18

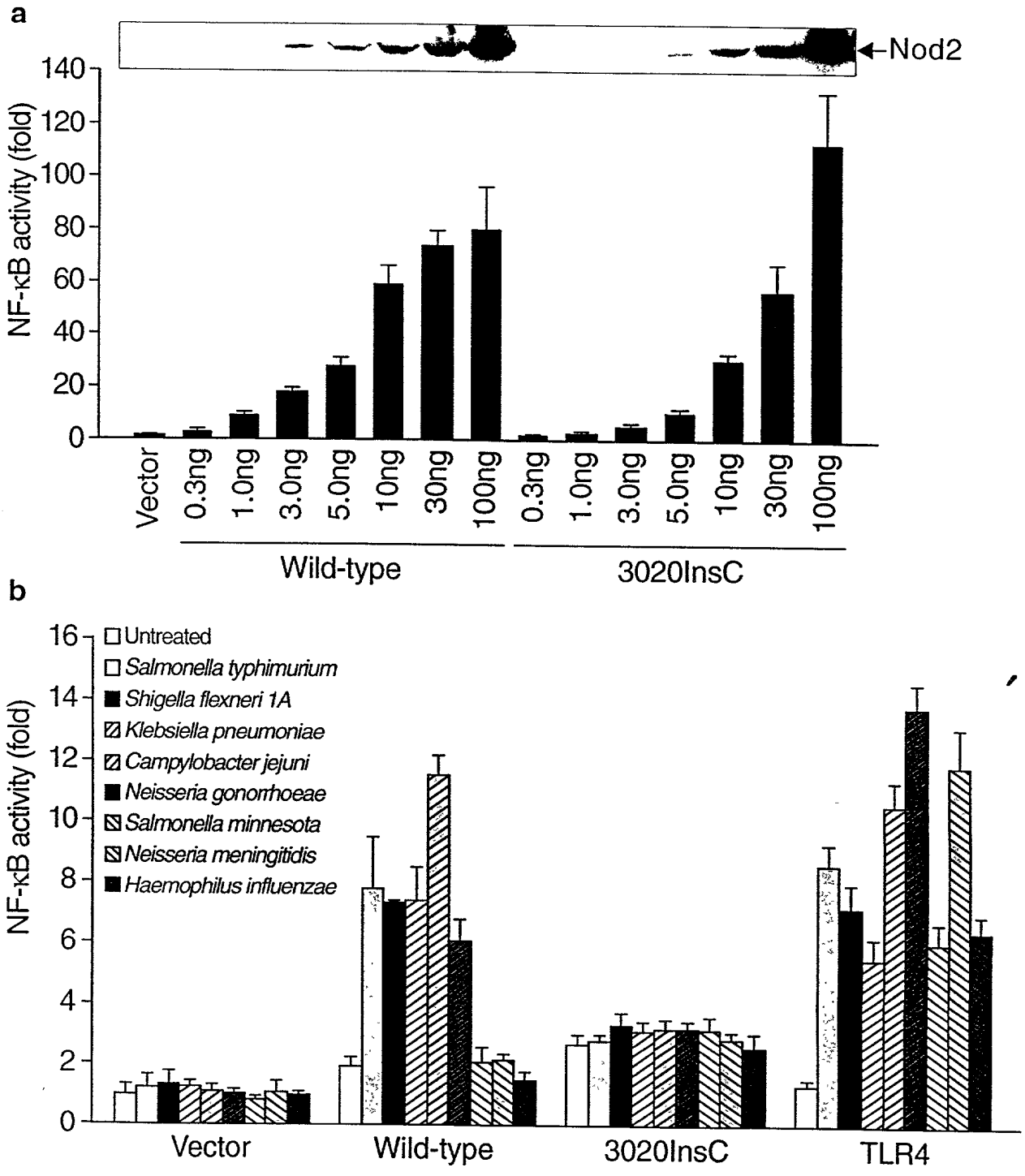

a
Nod2
NF-κB activity (fold)
140
120
100
80
60
40
20
0
Vector
0.3ng
1.0ng
3.0ng
5.0ng
10ng
30ng
100ng
Wild-type
3020InsC
b
Untreated
Salmonella typhimurium
Shigella flexneri 1A
Klebsiella pneumoniae
Campylobacter jejuni
Neisseria gonorrhoeae
Salmonella minnesota
Neisseria meningitidis
Haemophilus influenzae
NF-κB activity (fold)
16
14
12
10
8
6
4
2
0
Vector
Wild-type
3020InsC
TLR4

Figure 19

Figure 20
SEQ ID NO: 53

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tgccaaaggtgtcgtgccagggagtacggcgcccctggaattccttcacatcactttccagtgcttctttgccgcgttct
acctggcactcagtgctgatgtgccaccagctttgctcagacacctcttcaattgtggcaggccaggcaactcaccaatg
gccaggctcctgcccacgatgtgcatccaggcctcggagggaaaggacagcagcgtggcagctttgctgcagaaggccga
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cctgaagttgtccaataactgcatcacctacctaggggcagaagccctcctgcaggcccttgaaaggaatgacaccatcc
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tga

Figure 21
SEQ ID NO: 54

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tgcagagtcaccggccagccattgtcaggaggctccacagccatgtggagaacatgctggacctggcatgggagcggggt
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ttga

Figure 22
SEQ ID NO: 55

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120
GCWDPHSLHP ARDLQSHRPA IVRRLHSHVE NMLDLAWERG FVSQYECDEI RLPIFTPSQR
180
ARRLLDLATV KANGLAAFLL QHVQELPVPL ALPLEAATCK KYMAKLRTTV SAQSRFLSTY
240
DGAETLCLED IYTENVLEVW ADVGMAGSPQ KSPATLGLEE LFSTPGHLND DADTVLVVGE
300
AGSGKSTLLQ RLHLLWAAGQ DFQEFLFVFP FSCRQLQCMA KPLSVRTLLF EHCCWPDVGQ
360
EDIFQLLLDH PDRVLLTFDG FDEFKFRFTD RERHCSPTDP TSVQTLLFNL LQGNLLKNAR
420
KVVTSRPAAV SAFLRKYIRT EFNLKGFSEQ GIELYLRKRH HEPGVADRLI RLLQETSALH
480
GLCHLPVFSW MVSKCHQELL LQEGGSPKTT TDMYLLILQH FLLHATPPDS ASQGLGPSLL
540
RGRLPTLLHL GRLALWGLGM CCYVFSAQQL QAAQVSPDDI SLGFLVRAKG VVPGSTAPLE
600
FLHITFQCFF AAFYLALSAD VPPALLRHLF NCGRPGNSPM ARLLPTMCIQ ASEGKDSSVA
660
ALLQKAEPHN LQITAAFLAG LLSREHWGLL AECQTSEKAL LRRQACARWC LARSLRKHFH
720
SIPPAAPGEA KSVHAMPGFI WLIRSLYEMQ EERLARKAAR GLNVGHLKLT FCSVGPTECA
780
ALAFVLQHLR RPVALQLDYN SVGDIGVEQL LPCLGVCKAL YLRDNNISDR GICKLIECAL
840
HCEQLQKLAL FNNKLTDGCA HSMAKLLACR QNFLALRLGN NYITAAGAQV LAEGLRGNTS
900
LQFLGFWGNR VGDEGAQALA EALGDHQSLR WLSLVGNNIG SVGAQALALM LAKNVMLEEL
960
CLEENHLQDE GVCSLAEGLK KNSSLKILKL SNNCITYLGA EALLQAP*
1007

Figure 23
SEQ ID NO: 56

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ccaagaagcccaggccgacagccagtcccccaagctgcatggctgctgggacccccactcgctccacccagcccgagacc
tgcagagtcaccggccagccattgtcaggaggctccacagccatgtggagaacatgctggacctggcatgggagcggggt
ttcgtcagccagtatgaatgtgatgaaatcaggttgccgatcttcacaccgtcccagagggcaagaaggctgcttgatct
tgccacggtgaaagcgaatggattggctgccttccttctacaacatgttcaggaattaccagtcccattggccctgcctt
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acccccgcagaagagcccagccaccctgggcctggaggagctcttcagcacccctggccacctcaatgacgatgcggaca
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gccaggctcctgcccacgatgtgcatccaggcctcggagggaaaggacagcagcgtggcagctttgctgcagaaggccga
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tccatcccgccagctgcaccgggtgaggccaagagcgtgcatgccatgcccgggttcatctggctcatccggagcctgta
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cctgaagttgtccaataactgcatcacctacctaggggcagaagccctcctgcaggcccttgaaaggaatgacaccatcc
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tga

Figure 24
SEQ ID NO: 57

MGEEGGSASHDEEERASVLLGHSPGCEMCSQEAFQAQRSQLVELLVSGSLEGFESVLDWLLSWEVLSWEDYEGFHLLGQP
LSHLARRLLDTVWNKGTWACQKLIAAAQEAQADSQSPKLHGCWDPHSLHPARDLQSHRPAIVRRLHSHVENMLDLAWERG
FVSQYECDEIRLPIFTPSQRARRLLDLATVKANGLAAFLLQHVQELPVPLALPLEAATCKKYMAKLRTTVSAQSRFLSTY
DGAETLCLEDIYTENVLEVWADVGMAGPPQKSPATLGLEELFSTPGHLNDDADTVLVVGEAGSGKSTLLQRLHLLWAAGQ
DFQEFLFVFPFSCRQLQCMAKPLSVRTLLFEHCCWPDVGQEDIFQLLLDHPDRVLLTFDGFDEFKFRFTDRERHCSPTDP
TSVQTLLFNLLQGNLLKNARKVVTSRPAAVSAFLRKYIRTEFNLKGFSEQGIELYLRKRHHEPGVADRLIRLLQETSALH
GLCHLPVFSWMVSKCHQELLLQEGGSPKTTTDMYLLILQHFLLHATPPDSASQGLGPSLLRGRLPTLLHLGRLALWGLGM
CCYVFSAQQLQAAQVSPDDISLGFLVRAKGVVPGSTAPLEFLHITFQCFFAAFYLALSADVPPALLRHLFNCGRPGNSPM
ARLLPTMCIQASEGKDSSVAALLQKAEPHNLQITAAFLAGLLSREHWGLLAECQTSEKALLWRQACARWCLARSLRKHFH
SIPPAAPGEAKSVHAMPGFIWLIRSLYEMQEERLARKAARGLNVGHLKLTFCSVGPTECAALAFVLQHLRRPVALQLDYN
SVGDIGVEQLLPCLGVCKALYLRDNNISDRGICKLIECALHCEQLQKLALFNNKLTDGCAHSMAKLLACRQNFLALRLGN
NYITAAGAQVLAEGLRGNTSLQFLGFWGNRVGDEGAQALAEALGDHQSLRWLSLVGNNIGSVGAQALALMLAKNVMLEEL
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*

Figure 25
SEQ ID NO: 58

atgggggaagagggtggttcagcctctcacgatgaggaggaaagagcaagtgtcctcctcggacattctccgggttgtga
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tgcagagtcaccggccagccattgtcaggaggctccacagccatgtggagaacatgctggacctggcatgggagcggggt
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acccccgcagaagagcccagccaccctgggcctggaggagctcttcagcacccctggccacctcaatgacgatgcggaca
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gccaggctcctgcccacgatgtgcatccaggcctcggagggaaaggacagcagcgtggcagctttgctgcagaaggccga
gccgcacaaccttcagatcacagcagccttcctggcagggctgttgtcccgggagcactggggcctgctggctgagtgcc
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aattgactgacggctgtgcacactccatggctaagctccttgcatgcaggcagaacttcttggcattgaggctggggaat
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gcgcaacagagtgggtgacgagggggcccaggccctggctgaagccttgggtgatcaccagagcttgaggtggctcagcc
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cctgaagttgtccaataactgcatcacctacctaggggcagaagccctcctgcaggcccttgaaaggaatgacaccatcc
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tga

SNP	Allele	SNP Sequence*	AA Polymorphism	AA Location	cDNA Location		
SNP4	1	GGCAGATGTGGGCATGGCTGGACCC; SEQ ID NO:70	P	P 268 S	nt 802		
	2	GGCAGATGTGGGCATGGCTGGATCC; SEQ ID NO:71	S				
SNP20	1	AGACATCTGAGAAGGCCCTGCTCCGG; SEQ ID NO:72	R	R 702 W	nt 2104		
	2	AGACATCTGAGAAGGCCCTGCTCTGG; Seq ID NO:73	W				
SNP7	1	CTGCAGCACCTCCGGCGGCCCGTG: SEQ ID NO:74	V	V 793 M	nt 2377		
	2	CTGCAGCACCTCCGGCGGCCCATG; SEQ ID NO:75	M				
SNP18	1	TTGCAGAAGTTAGCTCTATTCAAC; SEQ ID NO:76	N	N 852 S	nt 2555		
	2	TTGCAGAAGTTAGCTCTATTCAGC: SEQ ID NO:77	S				
SNP25	1	ACTGACGGCTGTGCACACTCCATG; SEQ ID NO:78	M	M 863 V	nt 2587		
	2	ACTGACGGCTGTGCACACTCCGTG; SEQ ID NO:79	V				
SNP17	1	TGCAGTTCCTGGGATTCTGGGGC; SEQ ID NO:80	G	G 908 R	nt 2722		
	2	TGCAGTTCCTGGGATTCTGGCGC; SEQ ID NO:81	R				
SNP23	1	CACTGATGCTGGCAAAGAACGTC; SEQ ID NO:82	V	V 955 I	nt 2863		
	2	CACTGATGCTGGCAAAGAACATC; SEQ ID NO:83	I				
3020C ins	1	GGGCAGAAGCCCTCCTGCAGGCCCT; SEQ ID NO:90	wild-type		nt 3020		
	2	GGGCAGAAGCCCTCCTGCAGGCCCCT; SEQ ID NO:91	frameshift mutation	Δ33			
		*Underlined is mutated base					
		*Nucleotide/amino acid numbers designate the positions in Nod2a as reported by Ogura et al. J. Biol. Chem. 276:4812 [2001]					
		AA = amino acid					
		SNP= single nucleotide polymorphism					

Figure 26

snp4	snp20	snp7	snp18	snp17	snp23	3020insC	comment
1	1	1	1	1	1	1	common
2	1	1	1	1	1	1	about 10% allele frequency in controls
2	2	1	1	1	1	1	about 4% allele frequency in controls
2	1	1	1	2	1	1	about 1-2% allele frequency in controls
2	1	1	1	1	1	2	about 3-4% allele frequency in controls
1	1	1	1	1	1	1	very rare: 4/400 patients are heterozygous; occurs on allele 1 of snp4
1	1	2	1	1	1	1	very rare: arms not working
2	1	1	2	1	1	1	very rare: arms working
1	1	1	1	1	2	1	very rare; arms working

Figure 27

Figure 28
SEQ ID NO: 59

MGEEGGSASHDEEERASVLLGHSPGCEMCSQEAFQAQRSQLVELLVSGSLEGFESVLDWLLSWEVLSWEDYEGFHLLGQP
LSHLARRLLDTVWNKGTWACQKLIAAAQEAQADSQSPKLHGCWDPHSLHPARDLQSHRPAIVRRLHSHVENMLDLAWERG
FVSQYECDEIRLPIFTPSQRARRLLDLATVKANGLAAFLLQHVQELPVPLALPLEAATCKKYMAKLRTTVSAQSRFLSTY
DGAETLCLEDIYTENVLEVWADVGMAGPPQKSPATLGLEELFSTPGHLNDDADTVLVVGEAGSGKSTLLQRLHLLWAAGQ
DFQEFLFVFPFSCRQLQCMAKPLSVRTLLFEHCCWPDVGQEDIFQLLLDHPDRVLLTFDGFDEFKFRFTDRERHCSPTDP
TSVQTLLFNLLQGNLLKNARKVVTSRPAAVSAFLRKYIRTEFNLKGFSEQGIELYLRKRHHEPGVADRLIRLLQETSALH
GLCHLPVFSWMVSKCHQELLLQEGGSPKTTTDMYLLILQHFLLHATPPDSASQGLGPSLLRGRLPTLLHLGRLALWGLGM
CCYVFSAQQLQAAQVSPDDISLGFLVRAKGVVPGSTAPLEFLHITFQCFFAAFYLALSADVPPALLRHLFNCGRPGNSPM
ARLLPTMCIQASEGKDSSVAALLQKAEPHNLQITAAFLAGLLSREHWGLLAECQTSEKALLRRQACARWCLARSLRKHFH
SIPPAAPGEAKSVHAMPGFIWLIRSLYEMQEERLARKAARGLNVGHLKLTFCSVGPTECAALAFVLQHLRRPVALQLDYN
SVGDIGVEQLLPCLGVCKALYLRDNNISDRGICKLIECALHCEQLQKLALFNNKLTDGCAHSMAKLLACRQNFLALRLGN
NYITAAGAQVLAEGLRGNTSLQFLGFWRNRVGDEGAQALAEALGDHQSLRWLSLVGNNIGSVGAQALALMLAKNVMLEEL
CLEENHLQDEGVCSLAEGLKKNSSLKILKLSNNCITYLGAEALLQALERNDTILEVWLRGNTFSLEEVDKLGCRDTRLLL
*

Figure 29
SEQ ID NO: 60

atgggggaagagggtggttcagcctctcacgatgaggaggaaagagcaagtgtcctcctcggacattctccgggttgtga
aatgtgctcgcaggaggcttttcaggcacagaggagccagctggtcgagctgctggtctcagggtccctggaaggcttcg
agagtgtcctggactggctgctgtcctgggaggtcctctcctgggaggactacgagggcttccacctcctgggccagcct
ctctcccacttggccaggcgccttctggacaccgtctggaataagggtacttgggcctgtcagaagctcatcgcggctgc
ccaagaagcccaggccgacagccagtcccccaagctgcatggctgctgggacccccactcgctccacccagcccgagacc
tgcagagtcaccggccagccattgtcaggaggctccacagccatgtggagaacatgctggacctggcatgggagcggggt
ttcgtcagccagtatgaatgtgatgaaatcaggttgccgatcttcacaccgtcccagagggcaagaaggctgcttgatct
tgccacggtgaaagcgaatggattggctgccttccttctacaacatgttcaggaattaccagtcccattggccctgcctt
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aaagaccactacagatatgtacctgctgattctgcagcattttctgctgcatgccacccccccagactcagcttcccaag
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tgccaaaggtgtcgtgccagggagtacggcgccccctggaattccttcacatcactttccagtgcttctttgccgcgttct
acctggcactcagtgctgatgtgccaccagctttgctcagacacctcttcaattgtggcaggccaggcaactcaccaatg
gccaggctcctgcccacgatgtgcatccaggcctcggagggaaaggacagcagcgtggcagctttgctgcagaaggccga
gccgcacaaccttcagatcacagcagccttcctggcagggctgttgtcccgggagcactggggcctgctggctgagtgcc
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tccatcccgccagctgcaccgggtgaggccaagagcgtgcatgccatgcccgggttcatctggctcatccggagcctgta
cgagatgcaggaggagcggctggctcggaaggctgcacgtggcctgaatgttgggcacctcaagttgacattttgcagtg
tgggccccactgagtgtgctgccctggcctttgtgctgcagcacctccggcggcccgtggccctgcagctggactacaac
tctgtgggtgacattggcgtggagcagctgctgccttgccttggtgtctgcaaggctctgtatttgcgcgataacaatat
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aattgactgacggctgtgcacactccatggctaagctccttgcatgcaggcagaacttcttggcattgaggctggggaat
aactacatcactgccgcgggagcccaagtgctggccgagggctccgaggcaacacctccttgcagttcctgggattctg
gggcaacagagtgggtgacgagggggcccaggccctggctgaagccttgggtgatcaccagagcttgaggtggctcagcc
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cctgaagttgtccaataactgcatcacctacctaggggcagaagccctcctgcaggccccttgaaaggaatgacaccatcc
tggaagtctggctccgagggaacactttctctctagaggaggttgacaagctcggctgcagggacaccagactcttgctt
tga

Figure 30
SEQ ID NO: 61

MGEEGGSASHDEEERASVLLGHSPGCEMCSQEAFQAQRSQLVELLVSGSLEGFESVLDWLLSWEVLSWEDYEGFHLLGQP
LSHLARRLLDTVWNKGTWACQKLIAAAQEAQADSQSPKLHGCWDPHSLHPARDLQSHRPAIVRRLHSHVENMLDLAWERG
FVSQYECDEIRLPIFTPSQRARRLLDLATVKANGLAAFLLQHVQELPVPLALPLEAATCKKYMAKLRTTVSAQSRFLSTY
DGAETLCLEDIYTENVLEVWADVGMAGSPQKSPATLGLEELFSTPGHLNDDADTVLVVGEAGSGKSTLLQRLHLLWAAGQ
DFQEFLFVFPFSCRQLQCMAKPLSVRTLLFEHCCWPDVGQEDIFQLLLDHPDRVLLTFDGFDEFKFRFTDRERHCSPTDP
TSVQTLLFNLLQGNLLKNARKVVTSRPAAVSAFLRKYIRTEFNLKGFSEQGIELYLRKRHHEPGVADRLIRLLQETSALH
GLCHLPVFSWMVSKCHQELLLQEGGSPKTTTDMYLLILQHFLLHATPPDSASQGLGPSLLRGRLPTLLHLGRLALWGLGM
CCYVFSAQQLQAAQVSPDDISLGFLVRAKGVVPGSTAPLEFLHITFQCFFAAFYLALSADVPPALLRHLFNCGRPGNSPM
ARLLPTMCIQASEGKDSSVAALLQKAEPHNLQITAAFLAGLLSREHWGLLAECQTSEKALLRRQACARWCLARSLRKHFH
SIPPAAPGEAKSVHAMPGFIWLIRSLYEMQEERLARKAARGLNVGHLKLTFCSVGPTECAALAFVLQHLRRPVALQLDYN
SVGDIGVEQLLPCLGVCKALYLRDNNISDRGICKLIECALHCEQLQKLALFNNKLTDGCAHSMAKLLACRQNFLALRLGN
NYITAAGAQVLAEGLRGNTSLQFLGFWGNRVGDEGAQALAEALGDHQSLRWLSLVGNNIGSVGAQALALMLAKNVMLEEL
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*

Figure 31
SEQ ID NO: 62

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agagtgtcctggactggctgctgtcctgggaggtcctctcctgggaggactacgagggcttccacctcctgggccagcct
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tgcagagtcaccggccagccattgtcaggaggctccacagccatgtggagaacatgctggacctggcatgggagcggggt
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tga

Figure 32
SEQ ID NO: 63

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FVSQYECDEIRLPIFTPSQRARRLLDLATVKANGLAAFLLQHVQELPVPLALPLEAATCKKYMAKLRTTVSAQSRFLSTY
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Figure 33
SEQ ID NO: 64

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tga

Figure 34
SEQ ID NO: 65

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DFQEFLFVFPFSCRQLQCMAKPLSVRTLLFEHCCWPDVGQEDIFQLLLDHPDRVLLTFDGFDEFKFRFTDRERHCSPTDP
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SIPPAAPGEAKSVHAMPGFIWLIRSLYEMQEERLARKAARGLNVGHLKLTFCSVGPTECAALAFVLQHLRRPVALQLDYN
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Figure 35
SEQ ID NO: 66

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tga

Figure 36
SEQ ID NO: 67

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Figure 37
SEQ ID NO: 68

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tggaagtctggctccgagggaacactttctctctagaggaggttgacaagctcggctgcagggacaccagactcttgctt
tga

Figure 38
SEQ ID NO: 69

MGEEGGSASHDEEERASVLLGHSPGCEMCSQEAFQAQRSQLVELLVSGSLEGFESVLDWLLSWEVLSWEDYEGFHLLGQP
LSHLARRLLDTVWNKGTWACQKLIAAAQEAQADSQSPKLHGCWDPHSLHPARDLQSHRPAIVRRLHSHVENMLDLAWERG
FVSQYECDEIRLPIFTPSQRARRLLDLATVKANGLAAFLLQHVQELPVPLALPLEAATCKKYMAKLRTTVSAQSRFLSTY
DGAETLCLEDIYTENVLEVWADVGMAGPPQKSPATLGLEELFSTPGHLNDDADTVLVVGEAGSGKSTLLQRLHLLWAAGQ
DFQEFLFVFPFSCRQLQCMAKPLSVRTLLFEHCCWPDVGQEDIFQLLLDHPDRVLLTFDGFDEFKFRFTDRERHCSPTDP
TSVQTLLFNLLQGNLLKNARKVVTSRPAAVSAFLRKYIRTEFNLKGFSEQGIELYLRKRHHEPGVADRLIRLLQETSALH
GLCHLPVFSWMVSKCHQELLLQEGGSPKTTTDMYLLILQHFLLHATPPDSASQGLGPSLLRGRLPTLLHLGRLALWGLGM
CCYVFSAQQLQAAQVSPDDISLGFLVRAKGVVPGSTAPLEFLHITFQCFFAAFYLALSADVPPALLRHLFNCGRPGNSPM
ARLLPTMCIQASEGKDSSVAALLQKAEPHNLQITAAFLAGLLSREHWGLLAECQTSEKALLRRQACARWCLARSLRKHFH
SIPPAAPGEAKSVHAMPGFIWLIRSLYEMQEERLARKAARGLNVGHLKLTFCSVGPTECAALAFVLQHLRRPVALQLDYN
SVGDIGVEQLLPCLGVCKALYLRDNNISDRGICKLIECALHCEQLQKLALFNNKLTDGCAHSVAKLLACRQNFLALRLGN
NYITAAGAQVLAEGLRGNTSLQFLGFWGNRVGDEGAQALAEALGDHQSLRWLSLVGNNIGSVGAQALALMLAKNVMLEEL
CLEENHLQDEGVCSLAEGLKKNSSLKILKLSNNCITYLGAEALLQALERNDTILEVWLRGNTFSLEEVDKLGCRDTRLLL
*

Figure 39
SEQ ID NO: 84

atggggaagagggtggttcagcctctcacgatgaggaggaaagagcaagtgtcctcctcggacattctccgggttgtga
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agagtgtcctggactggctgctgtcctgggaggtcctctcctgggaggactacgagggcttccacctcctgggccagcct
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tggtggggaacaacattggcagtgtgggtgcccaagccttggcactgatgctggcaaagaacgtcatgctagaagaactc
tgcctggaggagaaccatctccaggatgaaggtgtatgttctctcgcagaaggactgaagaaaaattcaagtttgaaaat
cctgaagttgtccaataactgcatcacctacctaggggcagaagccctcctgcaggcccttgaaaggaatgacaccatcc
tggaagtctggctccgagggaacactttctctctagaggaggttgacaagctcggctgcagggacaccagactcttgctt
tga

Figure 40
SEQ ID NO: 85

MGEEGGSASHDEEERASVLLGHSPGCEMCSQEAFQAQRSQLVELLVSGSLEGFESVLDWLLSWEVLSWEDYEGFHLLGQP
LSHLARRLLDTVWNKGTWACQKLIAAAQEAQADSQSPKLHGCWDPHSLHPARDLQSHRPAIVRRLHSHVENMLDLAWERG
FVSQYECDEIRLPIFTPSQRARRLLDLATVKANGLAAFLLQHVQELPVPLALPLEAATCKKYMAKLRTTVSAQSRFLSTY
DGAETLCLEDIYTENVLEVWADVGMAGSPQKSPATLGLEELFSTPGHLNDDADTVLVVGEAGSGKSTLLQRLHLLWAAGQ
DFQEFLFVFPFSCRQLQCMAKPLSVRTLLFEHCCWPDVGQEDIFQLLLDHPDRVLLTFDGFDEFKFRFTDRERHCSPTDP
TSVQTLLFNLLQGNLLKNARKVVTSRPAAVSAFLRKYIRTEFNLKGFSEQGIELYLRKRHHEPGVADRLIRLLQETSALH
GLCHLPVFSWMVSKCHQELLLQEGGSPKTTTDMYLLILQHFLLHATPPDSASQGLGPSLLRGRLPTLLHLGRLALWGLGM
CCYVFSAQQLQAAQVSPDDISLGFLVRAKGVVPGSTAPLEFLHITFQCFFAAFYLALSADVPPALLRHLFNCGRPGNSPM
ARLLPTMCIQASEGKDSSVAALLQKAEPHNLQITAAFLAGLLSREHWGLLAECQTSEKALLRRQACARWCLARSLRKHFH
SIPPAAPGEAKSVHAMPGFIWLIRSLYEMQEERLARKAARGLNVGHLKLTFCSVGPTECAALAFVLQHLRRPVALQLDYN
SVGDIGVEQLLPCLGVCKALYLRDNNISDRGICKLIECALHCEQLQKLALFNNKLTDGCAHSMAKLLACRQNFLALRLGN
NYITAAGAQVLAEGLRGNTSLQFLGFWRNRVGDEGAQALAEALGDHQSLRWLSLVGNNIGSVGAQALALMLAKNVMLEEL
CLEENHLQDEGVCSLAEGLKKNSSLKILKLSNNCITYLGAEALLQALERNDTILEVWLRGNTFSLEEVDKLGCRDTRLLL
*

Figure 41
SEQ ID NO: 86

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cctgaagttgtccaataactgcatcacctacctaggggcagaagccctcctgcaggcccttgaaaggaatgacaccatcc
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tga

Figure 42
SEQ ID NO: 87

MGEEGGSASHDEEERASVLLGHSPGCEMCSQEAFQAQRSQLVELLVSGSLEGFESVLDWLLSWEVLSWEDYEGFHLLGQP
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FVSQYECDEIRLPIFTPSQRARRLLDLATVKANGLAAFLLQHVQELPVPLALPLEAATCKKYMAKLRTTVSAQSRFLSTY
DGAETLCLEDIYTENVLEVWADVGMAGSPQKSPATLGLEELFSTPGHLNDDADTVLVVGEAGSGKSTLLQRLHLLWAAGQ
DFQEFLFVFPFSCRQLQCMAKPLSVRTLLFEHCCWPDVGQEDIFQLLLDHPDRVLLTFDGFDEFKFRFTDRERHCSPTDP
TSVQTLLFNLLQGNLLKNARKVVTSRPAAVSAFLRKYIRTEFNLKGFSEQGIELYLRKRHHEPGVADRLIRLLQETSALH
GLCHLPVFSWMVSKCHQELLLQEGGSPKTTTDMYLLILQHFLLHATPPDSASQGLGPSLLRGRLPTLLHLGRLALWGLGM
CCYVFSAQQLQAAQVSPDDISLGFLVRAKGVVPGSTAPLEFLHITFQCFFAAFYLALSADVPPALLRHLFNCGRPGNSPM
ARLLPTMCIQASEGKDSSVAALLQKAEPHNLQITAAFLAGLLSREHWGLLAECQTSEKALLRRQACARWCLARSLRKHFH
SIPPAAPGEAKSVHAMPGFIWLIRSLYEMQEERLARKAARGLNVGHLKLTFCSVGPTECAALAFVLQHLRRPVALQLDYN
SVGDIGVEQLLPCLGVCKALYLRDNNISDRGICKLIECALHCEQLQKLALFSNKLTDGCAHSMAKLLACRQNFLALRLGN
NYITAAGAQVLAEGLRGNTSLQFLGFWGNRVGDEGAQALAEALGDHQSLRWLSLVGNNIGSVGAQALALMLAKNVMLEEL
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*

Figure 43
SEQ ID NO: 88

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agagtgtcctggactggctgctgtcctgggaggtcctctcctgggaggactacgagggcttccacctcctgggccagcct
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tgcagagtcaccggccagccattgtcaggaggctccacagccatgtggagaacatgctggacctggcatgggagcggggt
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tga

Figure 44
SEQ ID NO: 89

MGEEGGSASHDEEERASVLLGHSPGCEMCSQEAFQAQRSQLVELLVSGSLEGFESVLDWLLSWEVLSWEDYEGFHLLGQP
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FVSQYECDEIRLPIFTPSQRARRLLDLATVKANGLAAFLLQHVQELPVPLALPLEAATCKKYMAKLRTTVSAQSRFLSTY
DGAETLCLEDIYTENVLEVWADVGMAGSPQKSPATLGLEELFSTPGHLNDDADTVLVVGEAGSGKSTLLQRLHLLWAAGQ
DFQEFLFVFPFSCRQLQCMAKPLSVRTLLFEHCCWPDVGQEDIFQLLLDHPDRVLLTFDGFDEFKFRFTDRERHCSPTDP
TSVQTLLFNLLQGNLLKNARKVVTSRPAAVSAFLRKYIRTEFNLKGFSEQGIELYLRKRHHEPGVADRLIRLLQETSALH
GLCHLPVFSWMVSKCHQELLLQEGGSPKTTTDMYLLILQHFLLHATPPDSASQGLGPSLLRGRLPTLLHLGRLALWGLGM
CCYVFSAQQLQAAQVSPDDISLGFLVRAKGVVPGSTAPLEFLHITFQCFFAAFYLALSADVPPALLRHLFNCGRPGNSPM
ARLLPTMCIQASEGKDSSVAALLQKAEPHNLQITAAFLAGLLSREHWGLLAECQTSEKALLWRQACARWCLARSLRKHFH
SIPPAAPGEAKSVHAMPGFIWLIRSLYEMQEERLARKAARGLNVGHLKLTFCSVGPTECAALAFVLQHLRRPVALQLDYN
SVGDIGVEQLLPCLGVCKALYLRDNNISDRGICKLIECALHCEQLQKLALFNNKLTDGCAHSMAKLLACRQNFLALRLGN
NYITAAGAQVLAEGLRGNTSLQFLGFWGNRVGDEGAQALAEALGDHQSLRWLSLVGNNIGSVGAQALALMLAKNVMLEEL
CLEENHLQDEGVCSLAEGLKKNSSLKILKLSNNCITYLGAEALLQALERNDTILEVWLRGNTFSLEEVDKLGCRDTRLLL
*